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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,168	08/21/2001	Jennifer L. West	RICE 103	9212

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EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/935,168

Applicant(s)

WEST ET AL.

Examiner

" Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the corresponding address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 3-5 and 10-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-2, and 6-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6&7.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 1-23 are pending.
2. Applicant's election with traverse of Group I, Claims 1-2 and 6-9, drawn to a method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising enhancing molecule is TGF β , filed 10/9/02, is acknowledged. The traversal is on the grounds that (1) the independent claims are drawn to a Genus and the restriction requirement significantly narrows the scope of the claims absent of any prior art. This is not found persuasive because of the reasons set forth in the restriction mailed 9/24/02. In response to applicant that the absence of prior art, the examiner has no right narrow the claims, Applicants are reminded that the instant application is a US application and not a 371 of PCT and therefore no prior art is necessary for a restriction requirement. Further, the method of making and the method of using a product are drawn to distinct class and subclass. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group I and Groups II-XI is still deemed proper and is therefore made FINAL.
3. Claims 3-5 and 10-23 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 1-2 and 6-9, drawn to a method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising enhancing molecule is TGF β are being acted upon in this Office Action.
5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:
A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2, and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/23740 (Oct 1994, PTO 1449) in view of Dinbergs *et al* (J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGF β or TGF β 2 covalently crosslinked to a polymer matrix such as polyethylene glycol having a molecule weight such as 5000 (M-S-PEG 5000) which is between 2000 and 6000 via tethers such as succinimydyl succinate and is in a density of 5.2 (See page 12, line 11, PEG-TGF- β conjugates, rhTGF- TGF- β 2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGF β to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The claimed invention in claim 1 differs from the reference only that the method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising coupling matrix-enhancing molecules to the scaffold in an effective density to elicit production of extracellular matrix without increasing cellular proliferation wherein the matrix enhancing molecules are TGF- β is in a density between 1 and 100 ng/ml or in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

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The claimed invention in claim 2 differs from the reference only that the method further comprising attaching cells to the scaffold.

The claimed invention in claim 7 differs from the reference only that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 8 differs from the reference only that the method wherein the hydrogel is a formed of a polymer selected from the group consisting of alginate, collagen, hyaluronic acid and polyethylene glycol polymers.

The claimed invention in claim 9 differs from the reference only that the method wherein the matrix enhancing molecules are TGF- β is in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGF β in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGF β is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGF β has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGF β is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF-beta-2 or the polyethylene glycol as taught by the WO 94/23740 publication for the TGF β at a concentration of 1-10 ng/ml or the hydrogel such as alginate as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells bound to the scaffold as taught by the WO 94/23740 publication and Dinbergs *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

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One having ordinary skill in the art would have been motivated to do this because the WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGF β to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular). Dinbergs *et al* teach TGF β is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The term about is open-ended. It expands the claimed concentration to include the reference concentration of 1-10 ng/ml, which is about 4×10^{-6} to 4×10^{-3} nmol/ml. It is within the purview of one skilled in the art to apply the effective amount of TGF β for inducing the formation of extra-cellular matrix without increasing cellular proliferation as taught by Dinbergs *et al*.

9. Claims 1-2, and 6-9 are rejected under 35 U.S.C. 102(b) as being unpatentable over WO 96/27657 (Sept 1996; PTO 1449) in view of Dinbergs *et al* (J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGF β (see page 10, claim 25 of WO 96/27657 publication, in particular) flexibly linked or tethers (See page 6, line 11, page 12, Attachment methods, in particular) using carbodiimides as cross-linker to a polymer matrix such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, alginate, (See page 17, line 8, in particular) which all inherently have a molecular weight between 2000 and 5000 (See claims 22-23 of WO 96/27657 publication, in particular). The reference method further attaching cells to the reference scaffold (See page 16, line 7, in particular) for constructing tissue regeneration such as production of extracellular matrix proteins such as collagen (See page 17, line 1-4, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

The claimed invention in claims 1 and 9 differs from the reference only that the method for wherein the matrix enhancing molecules are TGF- β is in a density between 1 and 100 ng/ml or in a concentration between about 4×10^{-6} to 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling

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various matrix-enhancing molecule such as bFGF or TGF β in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGF β is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGF β has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogels such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGF β is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include TGF β at a concentration of about 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells bound to the scaffold as taught by the WO 96/27657 publication and Dinbergs *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular). Dinbergs *et al* teach TGF β is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The term about is open-ended. It expands the claimed concentration to include the reference concentration of 1-10 ng/ml, which is about 4×10^{-6} to 4×10^{-3} nmol/ml. It is within the purview of one skilled in the art to apply the effective amount of TGF β for inducing the formation of extra-cellular matrix without increasing cellular proliferation as taught by Dinbergs *et al*.

10. No claim is allowed.

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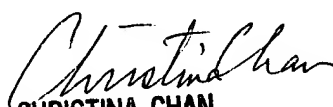
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
12. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

December 2, 2002


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